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Osteoprotegerin and its ligand: A new paradigm for regulation of osteoclastogenesis and bone resorption.

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In just 3 years, striking new advances have been made in understanding the molecular mechanisms that govern the crosstalk between osteoblasts/stromal cells and hemopoietic osteoclast precursor cells that leads to osteoclastogenesis. Led first by the discovery of osteoprotegerin (OPG), a naturally occurring protein with potent osteoclastogenesis inhibitory activity, rapid progress was made to the isolation of RANKL, a transmembrane ligand expressed on osteoblasts/stromal cells, that binds to RANK, a transmembrane receptor on hemopoietic osteoclast precursor cells. The interaction of RANK and RANKL initiates a signaling and gene expression cascade that results in differentiation and maturation of osteoclast precursor cells to active osteoclasts capable of resorbing bone. Osteoprotegerin acts as a decoy receptor; it binds to RANKL and blocks its interaction with RANK, thus inhibiting osteoclast development. Many of the calciotropic hormones and cytokines, including vitamin D3, parathyroid hormone, prostaglandin E2 and interleukin-11, appear to stimulate osteoclastogenesis through the dual action of inhibiting production of OPG and stimulating production of RANKL. Estrogen, on the other hand, appears to inhibit production of RANKL and RANKL-stimulated osteoclastogenesis. Recently, the results of the first clinical trial with OPG supported its potential as a therapeutic agent for osteoporosis. The new understanding provided by the RANK/RANKL/OPG paradigm for both differentiation and activation of osteoclasts has had tremendous impact on the field of bone biology and has opened new avenues for development of possible treatments of diseases characterized by excessive bone resorption.

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